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STUDIES ON THE QUANTITATIVE ESTIMATION OF ALKALOIDS BY MEANS OF IMMISCIBLE SOLVENTS

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of error, except in the extraction of certain alkaloids with ether. And finally, the shaking out of the alkaloidal solution in organic solvent introduces the problem of the possible insolubility of the salt formed in the acid solution or, if not its insolubility, its slow solubility. This is very apparent in the case of the salts of strychnine.

It is the purpose of this work to obtain such results as will describe the partition of the alkaloid between the acid layer and the immiscible solvent, using different acids under different concentration conditions. In order to obtain more complete data, the equilibrium conditions were determined, starting with an acid solution of the alkaloid and, as well, shaking out the solution of the alkaloid in organic solvent with an acid. Thus it is hoped that the following conditions might be established for each alkaloid:

(*a*) Which salt is most insoluble in chloroform or ether, and what concentration of acid is most favorable to this condition.

(*b*) Which acid, and in what concentration, removes the alkaloid most completely from its solution in chloroform or ether.

In order to put the results obtained in the form most quickly available, a new term, that of *extraction factor,* has been introduced and the factor calculated for the different sets of conditions obtained in the course of the research. By *extraction factor* is meant the ratio of the amount of alkaloid in the layer of added solvent to the amount originally present in the first solution. For practical purposes, this would be a far better value to have than that of the partition ratio or the sum of the partition ratios for the different alkaloidal molecular species present. The extraction factor shows at a glance the completeness of the extraction, an indication of the value of extraction under those conditions. The partition ratio tells only the partition of one molecular species between two layers of equal volume, by definition of the term *partition ratio.*

II. HISTORICAL.

Attention was first called to the quantitative solution of the problem through an article published by Dr. C. Kippenberger[3] in 1897. In this paper he states clearly the possibilities of error in alkaloidal estimation through hydrolysis of the salt with the subsequent solution of the free alkaloid. He suggests the use of chloroform or chloroform containing a little alcohol as solvents.

Three years later Kippenberger[4] published a second paper, in which he endeavored to establish the question on a firmer basis. He worked with the alkaloids strychnine, brucine, atropine, morphine, aconitine, veratrine, papaverine, narceine, codeine, emetine, pelletierine, cocaine, quinine, narcotine, coniine, sparteine, thebaine, hyoscyamine, daturine, scopolamine and the base caffeine. For shaking out he used chloroform and ether.

The action of the salts of the following acids was studied: Hydrochloric acid, 21.9 percent HCl; sulphuric acid, 40.1 percent H_2SO_4; tartaric acid; oxalic acid. In some cases, sodium chloride was added to the acid solution and its effect observed.

The alkaloid was dissolved with an excess of acid in 70 Cc. of water, and 50 Cc. of the immiscible solvent added. This mixture was shaken in a separatory funnel for about three minutes. After fully clearing, the layers were separated and the chloroform or ether layer washed with a few Cc. of water. The organic solvent was then evaporated on a water-bath and the residue, alkaloid plus alkaloidal salt, dried over concentrated sulphuric acid. The amounts of alkaloid and alkaloidal salt were determined in the following manner; the residue was dissolved

in an excess of $\frac{N}{50}$ standard acid and the excess acid titrated back with $\frac{N}{50}$ standard alkali. This value for acid neutralized by alkaloid indicated the amount of free alkaloid present in the residue. The solution was then made alkaline with a slight excess of sodium hydroxide and extracted again with chloroform. The amount of total alkaloid was obtained by evaporation of the solvent and solution of the residue in standard acid with titration for excess acid as before. Subtraction of the first value, that of the free alkaloid from the second, or total alkaloid value will give the amount of alkaloid present in the residue as salt.

The results are found in the following tables. The column containing the strength of acidity was compiled by the authors of this paper, from the data of Kippenberger.

TABLE I.

EXTRACTION OF AN ALKALOID BY CHLOROFORM FROM ITS SOLUTION IN HYDROCHLORIC ACID (KIPPENBERGER).

Alkaloid solution in 70 Cc. water.	Amount of alkaloid in 50 Cc. $CHCl_3$.	Indicator.	Strength of acid.	Alkaloid. Free.	Alkaloid. Salt.
Gm.					
0.2 Strychnine	0.0910	Azolitmin	0.15N	0.0114	0.0806
0.2 Brucine	0.0798	Azolitmin	0.075N	0.0056	0.0742
0.2 Atropine	0.0014	Azolitmin	0.075N		
0.2 Morphine	.....	Azolitmin	0.075N		
0.2 Aconitine	0.0971	Azolitmin	0.03N	0.0158	0.0813
0.2 Veratrine	0.0807	Azolitmin	0.075N	0.0077	0.0730
0.2 Codeine	Trace	Azolitmin	0.03N		
0.2 Cocaine	0.0021	Azolitmin	0.015N		
0.2 Quinine	Trace	Azolitmin	0.03N		

TABLE II.

EXTRACTION OF AN ALKALOID BY CHLOROFORM FROM ITS SOLUTION IN SULPHURIC ACID (KIPPENBERGER).

Alkaloid solution in 70 Cc. water.	Amount of alkaloid in 50 Cc. $CHCl_3$.	Indicator.	Strength of acid.	Alkaloid. Free.	Alkaloid. Salt.
Gm.					
0.2 Strychnine	Trace	Azolitmin	0.17N		
0.2 Brucine	0.0020	Azolitmin	0.17N		
0.2 Atropine	.....	Azolitmin	0.034N		
0.2 Morphine	.....	Azolitmin	0.034N		
0.2 Aconitine	0.0120	Azolitmin	0.017N	0.0120	
	0.0064	Azolitmin	0.085N	0.0064	
	Trace	Azolitmin	0.255N		
0.2 Veratrine	Trace	Azolitmin	0.017N		
0.2 Codeine	.....	Azolitmin	0.034N		
0.2 Quinine	.....	Azolitmin	0.034N		

TABLE III.

EXTRACTION OF AN ALKALOID BY CHLOROFORM FROM ITS SOLUTION IN A MIXTURE OF HYDROCHLORIC ACID AND SODIUM CHLORIDE (KIPPENBERGER).

Alkaloid solution in 70 Cc. water.	Amount of alkaloid in 50 Cc. $CHCl_3$.	Indicator.	Strength of acid.	Alkaloid. Free.	Alkaloid. Salt.
Gm.					
0.2 Atropine, 14 Cc. NaCl	0.0192	Azolitmin	0.075N	.....	Trace
0.2 Atropine, 14 Cc. NaCl	0.0149	Azolitmin	0.015N	.....	Trace
0.2 Quinine, 14 Cc. NaCl	0.0100	Hæmatoxylin	0.03N	0.0037	Acid salt
				0.0063	Neutral salt
0.2 Aconitine, 14 Cc. NaCl	0.2160	Azolitmin	0.017N	0.0306	0.1854
0.2 Quinine	0.0057	Hæmatoxylin	0.03N	0.004	Acid salt
				0.0017	Neutral salt

TABLE IV.

EXTRACTION OF AN ALKALOID BY CHLOROFORM FROM ITS SOLUTION IN TARTARIC ACID (KIPPENBERGER).

Alkaloid solution in 70 Cc. water.	Amount of alkaloid in 50 Cc. $CHCl_3$.	Indicator.	Strength of acid.	Alkaloid. Free.	Alkaloid. Salt.
Gm.					
0.2 Strychnine..... 0.4 Tartaric Acid.....	0.0020	Azolitmin	.....		
0.4 Brucine..... 0.4 Tartaric Acid.....	0.0032	Azolitmin	.....		

TABLE V.

RESULTS OF SHAKING OUT THE ACID ALKALOIDAL SOLUTION WITH ETHER, UNDER THE SAME CONDITIONS AS BEFORE (KIPPENBERGER).

FROM HYDROCHLORIC ACID SOLUTION.

Ether took up:

Narcotine.....0.0002 grammes.

Caffeine.....0.0112 grammes, as free caffeine.

The following were found in noticeable traces:

Aconitine, narceine, and emetine.

None of the other alkaloids gave up a trace to ether.

FROM SULPHURIC ACID SOLUTION.

Ether took up:

Caffeine.....0.0083 grammes as free caffeine.

The following were found in noticeable amounts:

Aconitine, papaverine, narceine, emetine and narcotine, also very slight traces of veratrine, strychnine, and codeine.

THE ADDITION OF SODIUM CHLORIDE TO THE SOLUTIONS GAVE THE FOLLOWING RESULTS:

(*a*) From hydrochloric acid in noticeable traces:

Narcotine, atropine, and quinine.

(*b*) From sulphuric acid solution:

Aconitine.

Ether removed neither brucine nor strychnine from tartaric acid solutions.

In 1901, Hans Proelss[5] gave a short description of the behavior of alkaloidal solutions toward different solvents. The work was divided in two parts: The first to determine the best solvent for the alkaloids as a class, and the second, the best solvent for the individual alkaloids. He compared the relative extractive powers of ether, chloroform, and benzene, and also mixtures of ether and chloroform, and alcohol and chloroform, for the alkaloids picrotoxin, veratrine, strychnine, atropine, codeine, and morphine. His method consisted in dissolving 0.1 gramme of alkaloid in 50 Cc. of water containing a few drops of hydrochloric acid. After making alkaline with sodium carbonate, the aqueous solution was extracted three times with the solvent. He states that constant results could not be obtained of sufficient accuracy to be anything more than comparative.

1. THE BEST SOLVENT FOR ALKALOIDS IN GENERAL.

Solvent.	Results.
Ether	Very good with colchicine, brucine.
Chloroform	Very good with colchicine, brucine, digitalin, veratrine, atropine, strychnine.
Chloroform and ether	Very good with colchicine, atropine, veratrine, picrotoxin.
Chloroform and alcohol	Very good with colchicine, veratrine, digitalin, atropine, codeine, morphine plus potassium bicarbonate.
Benzene	Very good with colchicine, strychnine, atropine, codeine, picrotoxin.

In conclusion he states that the best shaking-out liquid for alkaloids in general is chloroform, because of the solubility of most of the alkaloids in chloroform.

2. The Best Shaking-out Liquid for the Individual Alkaloids.

Alkaloids.	Results.
Atropine	Any solvent satisfactory.
Brucine	Same as for picrotoxin.
Codeine	Alcohol plus chloroform, benzene.
Colchicine	Any solvent satisfactory.
Morphine	Alcohol plus chloroform from potassium carbonate solution.
Picrotoxin	Ether, chloroform from sodium carbonate-ammonium hydroxide solution.
Strychnine	Chloroform, alcohol plus chloroform, benzene from sodium carbonate-ammoniacal solution.
Veratrine	Chloroform, ether plus chloroform, ether and benzene from ammoniacal solution.

In conclusion, he states that emulsions form easiest with benzene and least with ether.

Ed. Springer,[6] in 1902, studied the effect of the solvent chloroform on the extraction of the following alkaloids: Morphine, coniine, narcotine, strychnine, quinine, codeine, veratrine, and cocaine from solutions made acid with sulphuric, phosphoric, hydrochloric, tartaric, acetic, oxalic and citric acids.

The amount of alkaloid in the residue after evaporation of chloroform was determined by titration in the same way that Kippenberger did. For some reason, he was unable to obtain check results, and so his work is of no value from a quantitative stand-point.

The following are his results:

Aconitine.—Aconitine is removed as the salt from hydrochloric acid and as the pure salt in traces from the sulphuric acid solution.

Atropine.—From hydrochloric acid, traces were removed as the salt; from sulphuric acid, traces as the free alkaloid; traces were found from the tartaric acid solution, also.

Cocaine.—Some alkaloid is extracted from sulphuric and hydrochloric acid solutions, where the acid is present in small concentration.

Codeine.—Codeine is not found in the chloroform residues from extraction of solutions of alkaloids in phosphoric, tartaric, oxalic, citric, and sulphuric acids, although in the last case it was found that if the concentration of the acid was low enough, some of the alkaloid would be removed as the free base.

Morphine, Coniine, and Nicotine.—No alkaloid was extracted from solutions made acid with the following acids: Hydrochloric, sulphuric and phosphoric.

Narcotine.—Narcotine is removed from both hydrochloric and sulphuric acid solutions, partly as base and partly as salt.

Quinine.—No alkaloid is removed from solutions of the sulphate, tartrate or phosphate. Some quinine is removed as the hydrochloride.

Strychnine.—About 25 percent was removed from the hydrochloric acid solution as the salt. Slight traces were removed from the other acid solutions.

Veratrine.—Veratrine is removed in traces in solutions containing small amounts of tartaric, sulphuric, and citric acids, but such is not the case with large excess of sulphuric or phosphoric acids.

From this, it may be drawn that chloroform is a "good solvent" for the hydrochloric acid salts of the alkaloids. The solubility of the hydrochlorides is so great, in fact, that, if in excess of acid, the salt is taken over completely as the salt, and

only in the case of the weak base narcotine could traces of the free alkaloid be found in the chloroform extract.

From the table, one would expect to find in the chloroform extract from the sulphuric acid solution in the Dragendorff assay, aconitine and narcotine, as well as the alkaloids mentioned by Dragendorff himself. Strychnine, veratrine and atropine might also be found in small amounts.

In 1906, Simmer[7] published an important paper on this subject. The work was divided in three parts:

1. The behavior of the salts of the common alkaloids toward extraction by chloroform and other important solvents.
2. The appearance of decomposition through treatment with chloroform.
3. The reducing action of the alkaloids.

Simmer prepared an aqueous solution of the alkaloidal salt, containing 0.2 gramme of the free alkaloid to 50 Cc. of solution, or 0.4 percent of the free alkaloid. He then acidified with the different acids until he obtained the desired concentrations. Simmer neglected to state definitely the amount of chloroform used in the extraction, but the general tone of the paper would lead one to believe that he used equal amounts of chloroform and aqueous solution. These were mixed and the extraction carried on for an hour. At the end of that time, the layers were separated and the chloroform evaporated. The amount of free alkaloid and alkaloidal salt was determined in the residue in the usual manner.

It will be seen from the tables that many neutral salts are extracted by both chloroform and benzene; this is especially true in the cases of the salts of the nitric and halogen acids.

With strychnine hydrochloride, the least amount of salt is extracted from the neutral solution and the most from the solution that contains a 10 percent excess of acid; the 25 percent acid gives up less alkaloid than the 10 percent solution.

The behavior of the weak bases colchicine, caffeine, narcotine, papaverine, and antipyrine is different. In strong hydrochloric acid solution of colchicine, there is as much alkaloid removed by the chloroform as from the aqueous solution. The same is true with sulphuric or phosphoric acid solutions. Caffeine, thebaine and narcotine are removed from weak tartaric acid solutions as easily as from stronger acid solutions. Papaverine, narcotine, and thebaine are removed simply as salts and not as free bases.

TABLE VI.

BEHAVIOR OF NEUTRAL AND ACIDIFIED ALKALOIDAL SALT SOLUTIONS TOWARD EXTRACTION WITH CHLOROFORM (SIMMER).

Alkaloidal salt.	Amount in 50 Gm. water.	Strength, acid per cent.	Grammes alkaloid. Total.	Free.	Salt.
Strychnine hydrochloride	0.2377	0.0	0.0153	0.0142	0.0016
	0.2377	0.1	0.0083	0	0.0083
	0.2377	1.0	0.0250	0	0.0250
	0.2377	10.0	0.0559	0	0.0559
	0.2377	25.0	0.2330	0	0.2330
Strychnine hydrobromide	0.2480	0.0	0.0200	0.0133	0.0067
	0.2480	0.1	0.0167	0	0.0167
	0.2480	1.0	0.0350	0	0.0350
Strychnine hydriodide	0.2760	0.0	0.0560	0.0250	0.0317
Strychnine nitrate	0.2377	0.0	0.0283	0.0233	0.0050
	0.2377	1.0	0.0350	0	0.0350
Strychnine sulphate	0.2610	0.0	Trace		
	0.2610	1.0	Trace		
Veratrine hydrochloride	0.2110	0.0	0.0530	0.0499	0.0031
	0.2110	0.1	0.0327	0	0.0327
	0.2110	10.0	0.1248	0	0.1248

TABLE VI.—*Continued.*

Alkaloidal salt.	Amount in 50 Gm. water.	Strength, acid per cent.	Grammes alkaloid. Total.	Free.	Salt.
Veratrine nitrate	0.2200	0.0	0.0405	0.0405	0
	0.2200	1.0	0.0811	0	0.0811
Veratrine sulphate	0.2150	0.0	0.0374	0.0374	0
	0.2150	0.1	Traces		
Veratrine tartrate	0.2230	0.1	0.0842	0.0842	0
	0.2230	2.0	0.0155	0.0155	0
	0.2230	5.0	Traces		
Morphine hydrochloride	0.2470	0.0	0.0045	0.0045	0
	0.2470	0.1	0	0	0
	0.2470	5.0	0	0	0
Morphine sulphate	0.2500	0.0	0.0037	0.0037	0
	0.2500	0.1	0	0	0
Morphine acetate	0.2630	0.0	0.0197	0.0197	0
Codeine hydrochloride	0.2340	0.0	0.0371	0.0371	0
	0.2340	0.1	0.0015	0	0.0015
	0.2340	10.0	0.0079	0	0.0079
Codeine hydrobromide	0.2620	0.0	0.0126	0.0126	0
	0.2620	0.1	Traces		
	0.2620	10.0	0.0110	0	0.0110
	0.2620	25.0	0.0079	0	0.0079
Codeine sulphate	0.2470	0.0	0.0276	0.0276	0
	0.2470	0.1	Traces		
Codeine tartrate	0.2360	0.1	0.0110	0.0110	0
Codeine citrate	0.2480	0.0	0.0395	0.0395	0
	0.2480	0.1	0.0158	0.0158	0
Cocaine hydrochloride	0.2240	0.0	0.0490	0.0490	0
	0.2240	0.1	0.0037	0.0015	0.0022
	0.2240	1.0	0.0045	0	0.0045
	0.2240	10.0	0.0075	0	0.0075
Cocaine sulphate	0.2640	0.0	0.0143	0.0143	0
	0.2640	0.1	Traces		
Cocaine tartrate	0.2310	0.0	0.0543	0.0543	0
	0.2310	0.1	0.0528	0.0528	0
	0.2310	1.0	0.0332	0.0332	0
	0.2310	5.0	0.0015	0.0015	0
Atropine hydrochloride	0.2250	0.0	Traces of free atropine.		
	0.2250	0.1	Traces of free atropine.		
	0.2250	10.0	0.0028	0	0.0028

TABLE VII.

BEHAVIOR OF NEUTRAL AND ACIDIFIED AKLALOIDAL SALT SOLUTIONS TOWARD EXTRACTION WITH BENZENE (SIMMER).

Alkaloidal salt.	Amount in 50 Gm. of water.	Strength, acid per cent.	Grammes alkaloid. Total.	Free.	Salt.
Strychnine hydrochloride	0.2377	0.0	0.0075	0.0075	0
	0.2377	0.1	0	0	0
	0.2377	1.0	0	0	0
	0.2377	10.0	Traces		
Strychnine hydrobromide	0.2480	0.0	0.0033	0.0033	0
	0.2480	0.1	Traces		
Strychnine hydriodide	0.2760	0.0	0.0033	0.0033	0
Strychnine sulphate	0.2610	0.0	0	0	0
Strychnine nitrate	0.2377	0.1	Traces		
Veratrine sulphate	0.2150	0.0	Traces		
	0.2150	0.1	Traces		
Codeine hydrochloride	0.2340	0.0	0.0055	0.0055	0
	0.2340	0.1	0	0	0
	0.2340	10.0	0	0	0
Codeine hydrobromide	0.2620	0.0	0.0023	0.0023	0
	0.2620	1.0	0	0	0
Codeine sulphate	0.2470	0.0	0.0031	0.0031	0
Codeine citrate	0.2480	0.0	0.0023	0.0023	0

2. THE DECOMPOSING POWER OF THE ALKALOIDS ON CHLOROFORM.

The observation had been made by many authors that extraction of the alkaloids with chloroform is attended with a decomposition of the chloroform, giving rise to free hydrochloric acid.

In order to determine this, Simmer extracted a mixture of 50 Gm. of water and 2 Gm. of finely powdered alkaloid with 50 Gm. of chloroform for eight hours. First the water was tested. This always gave an opalescence with silver nitrate, but showed itself to be free from alkaloid, except in the few cases due to the relative insolubility of the alkaloid in chloroform. The chloroform layer was then evaporated and the residue dissolved in water containing a sufficient amount of sulphuric acid. Silver nitrate solution was then added. When a definite precipitate was observed, this was filtered, dissolved in ammonia and precipitated again with nitric acid. Then the pure precipitate was filtered in a Gooch crucible and weighed.

TABLE VIII.

Alkaloid, 2 Gm.	AgCl from the chloroform layer.	Corresponding to—	
		HCl.	Alkaloid.
Atropine	0.0038	0.0009	0.0072
Brucine	0.0138	0.0033	0.0333
Quinine	Traces		
Cinchonidine	Traces		
Cinchonine	Traces		
Cocaine	0.0021	0.0005	0.0042
Codeine	Traces		
Morphine	0		
Narcotine	0		
Nicotine	Traces		
Strychnine	0.0035	0.0008	0.0073
Veratrine	0.0043	0.0010	0.0173

Thus we see that the action of the alkaloid upon the chloroform is negligible, except in the cases of brucine and veratrine.

Marden and Elliott,[8] in 1914, published a paper on the methods of extraction by immiscible solvents from the point of view of the distribution ratios. They shook out the alkaloids aconitine, atropine, codeine, coniine, morphine, quinine, and strychnine with the solvents chloroform and ether. Ammonium hydroxide was used to make the acid solution alkaline.

From the distribution coefficient and a certain subsequent algebraic calculation, they could determine the number of extractions necessary to remove 99.9 percent of the alkaloid. The distribution ratio (d) is indicated by the expression.

$$\frac{\text{Concentration in 10 Cc. of water}}{\text{Concentration in 10 Cc. of non-aqueous solvent}} = \frac{C}{C} = (d)$$

The algebraic expression for the calculation of the number of shakings necessary for an extraction is indicated by

$$\frac{x_n}{x_o} = \left(\frac{da}{e + da}\right)^n \text{ where}$$

a = volume of the aqueous solvent.
e = volume of non-aqueous solvent.
d = distribution ratio.
x_o = original amount of material to be extracted in the aqueous layer.
x_n = amount of material in the water layer after n extractions.

In the system aconitine, ether and aqueous ammoniacal solution, using 100 Cc. water, 5 Cc. ammonium hydroxide, and 50 Cc. of ether, the following result was obtained, $d = 0.140$; but on substituting 30 Cc. of chloroform for the 50 Cc. of ether, the value of d became 0.017.

Atropine.—The distribution ratio in the system water and chloroform was found to be very small and three extractions with 10 Cc. of chloroform from 50 Cc. of the aqueous solution were sufficient to remove the atropine.

Codeine.—In the system, 100 Cc. water, 5 Cc. ammonium hydroxide, and 50 Cc. ether, *d* had a value of 0.939. If 30 Cc. chloroform were substituted for the ether, the value became 0.0067.

Coniine.—Owing to the volatility of the coniine, it was very difficult to get the partition ratio.

Morphine.—In the system, saturated aqueous solution of potassium carbonate and a mixture of methyl alcohol and chloroform, *d* possessed a value of 0.154, with variations from 0.200 to 0.127. The value for the system, 100 Cc. water, containing 35 Gm. sodium chloride, and 45 Cc. of a 2:1 mixture of chloroform and ethyl alcohol was found to be 0.528.

The value for *d* between water and chloroform-amyl alcohol mixtures was 0.345.

Quinine.—Between water made alkaline with ammonium hydroxide and chloroform, quinine was found to possess such a low distribution coefficient that three washings of a 50 Cc. aqueous solution with 10 Cc. of chloroform were found to remove all of the alkaloid.

Strychnine.—The authors determined the distribution coefficients for systems containing chloroform alone and in a mixture with ether in order to see which would prove more efficient, as there has been a great difference of usage.

For the system, 100 Cc. of water, 2 Cc. of ammonium hydroxide, and 30 Cc. of chloroform, *d* was found to be equal to 0.003, but on substituting a mixture of 1:3 chloroform and ether, the value 0.087 was obtained.

Summary of the Historical Chapter.—In looking over the work that has been published on the subject of the quantitative estimation of the alkaloids by the shaking-out process, sufficient data will be found to establish the equilibrium conditions of the systems, alkaloidal hydrochlorides or sulphates between their acid solutions and chloroform or ether. Results are lacking, however, which will show the partition of alkaloidal tartrates between tartaric acid and those solvents.

In addition the whole subject of the extraction of an alkaloid from its solution in chloroform by an acid has never been investigated. If equilibrium is reached, this should give the same value as with the extraction of the acid salt solution by that solvent. In practice, it takes a long time with some of these systems and there are certain other factors entering in.

III. THEORETICAL CONSIDERATION.

In an acid solution of a neutral alkaloidal salt the following equilibria are established:

(*a*) The alkaloidal salt is in equilibrium with the free alkaloid and acid, due to the hydrolysis of the salt, and

(*b*) The neutral salt and acid are in equilibrium with an acid salt. It is possible that more than one acid salt may be formed, in which case there will be as many more equilibrium reactions as there are acid salts formed. If chloroform is added to this system, and the mixture shaken, each of these equilibria may be affected. For example, the mass law equation for the hydrolysis of an alkaloidal salt is expressed by the following:

$$\frac{C_{\text{alkaloid}} \times C_{\text{acid}}}{C_{\text{salt}} \times C_{\text{water}}} = k,$$

where k is the mass law constant. The removal of one of the constituents will cause a resultant shift in the other concentrations in order that k may remain constant. The presence of a great excess of acid will drive back the hydrolysis by increasing the value for the term C_{acid} with the resultant decrease in value for the term $C_{alkaloid}$. At the same time, solution of the alkaloid in chloroform will cause a decrease in the value, $C_{alkaloid}$, with a resultant further lowering of C_{salt} in order to restore equilibrium. This salt which is removed is hydrolyzed. So the result of the removal of free alkaloid is to increase the hydrolysis. Thus, in this system at equilibrium the conditions existing are a resultant of these two equilibria which are progressing with opposite tendencies.

To approach the equilibrium from the other direction, however, introduces a new factor, namely, the speed of solution of the newly-formed salt in acid solution. As the two immiscible layers are being shaken together, forming an intimate mixture of alkaloid dissolved in chloroform and acid in the water, the alkaloid molecule in the chloroform and the acid molecule in the aqueous acid liquid meet at the junction of these fine drops of the two solutions, and combine.

In case the acid is monobasic, the first result of the reaction is probably the formation of a neutral salt. In an excess of acid, the acid salt is then formed.

With the dibasic acids, however, such as tartaric acid or sulphuric acid, the acid salt is formed first, similarly to the mechanism of the neutralization of sulphuric acid with sodium hydroxide. As more alkaloid combines, there is a gradual change from the acid salt into the neutral salt. The neutral salt in many cases seems to be very slowly soluble at ordinary temperatures, although it goes easily into solution at boiling temperature. With the excess of acid, however, the first acid salt is formed, which in some cases is only slightly soluble in a small excess of acid. As the excess of acid becomes greater, the soluble higher acid salts are formed. Thus the solution in acid may be hastened by shaking out with fresh portions of acid, in order to get the alkaloid as the higher acid salt. This situation would not be met with where the salt solution is shaken with chloroform or ether, for in these cases the salt is dissolved at a much higher temperature and the solution cooled.

IV. EXPERIMENTAL.

(*a*) Preparation of some alkaloidal tartrates and a brief description of their properties:

The neutral salts were prepared by dissolving the alkaloids in an aqueous acid solution, containing equivalent amounts of tartaric acid in a large excess of water, at the boiling temperature. In the excess of hot water, the acid salt which forms first stays in solution and the remainder of the alkaloid completely neutralizes it. On cooling the solution slowly, the neutral salt comes out in beautiful crystals. In one or two cases it was necessary to evaporate some of the solvent water in order to get the right concentration for crystallization.

The mon-acid salt may be prepared by dissolving the alkaloid in a slight excess of acid, in a small quantity of hot water. On cooling the crystals of the acid salt will come out.

These salts are further purified by crystallization from water several times.

In this way the crystalline salts of brucine, cinchonine, cinchonidine, quinine, morphine, and strychnine were prepared. The alkaloids aconitine, atropine, cocaine, codeine, and veratrine were obtained in the form of tartrates for further investigation by simply dissolving the alkaloids in the proper concentration of acid, as their tartrate salts were amorphous.

The neutral salts are characterized as follows:

(The amount of alkaloid present represents the percent alkaloid in the anhydrous salt.)

Strychnine:

M. P. 226°–227°, browning at 215°.
Crystalline form: beautiful white rosettes.
Analysis: 81.68 percent strychnine.
15.00 percent water.
Theoretical for $(C_{21}H_{22}N_2O_2)_2.C_4H_6O_6.8H_2O$:
81.66 percent strychnine.
15.20 percent water.

Brucine:

M. P. 236°–237°, with decomposition; browns at 210°.
Crystalline form: white cubes.
Analysis: 83.2 percent brucine.
9.1 percent water.
Theoretical for $(C_{23}H_{26}N_2O_4)_2.C_4H_6O_6.5H_2O$:
83.7 percent brucine.
8.8 percent water.

Quinine:

M. P. 199°, with browning.
Crystalline form: fine white needles.
Analysis: 81.28 percent quinine.
2.56 percent water.
Theoretical for $(C_{20}H_{24}N_2O_2)_2.C_4H_6O_6.H_2O$:
81.20 percent quinine.
2.3 percent water.

Cinchonidine:

M. P. 230°–231° with decomposition; browns at 218°.
Crystalline form: long white needles.
Analysis: 79.68 percent cinchonidine.
4.60 percent water.
Theoretical for $(C_{19}H_{22}N_2O)_2.C_4H_6O_62H_2O$:
79.69 percent cinchonidine.
4.64 percent water.

Cinchonine:

M. P. 190°, without either decomposition or browning.
Crystalline form: short white needles.
Analysis: 79.76 percent cinchonine.
2.8 percent water.
Theoretical for $(C_{19}H_{22}N_2O)_2.C_4H_6O_6.H_2O$:
79.69 percent cinchonine.
2.4 percent water.

The water of crystallization was determined by weighing the sample, heating at 110° to constant weight, and then dissolving the anhydrous salt in water. The solution was made alkaline and extracted twice with an excess of chloroform. The chloroform was evaporated and the residue heated to constant weight. The value obtained was that of the weight of the alkaloid in the sample of salt taken. From

the value of alkaloid and that of water of crystallization was calculated the formula of the salt. The one exception in this procedure was in the case of brucine where the residue from the chloroform extraction of the alkaline brucine solution was dissolved in standard acid and the excess acid titrated back with standard alkali.

The acid salts were analyzed in the same manner.

(*b*) Determination of the equilibrium conditions for the partition of the alkaloids and alkaloidal salts between aqueous neutral and acid solutions and an immiscible solvent (chloroform or ether):

1. Extraction of the neutral or acid aqueous alkaloidal solution with chloroform and ether:

0.2 Gm. of the neutral alkaloidal salt was dissolved in 25 Cc. of the aqueous acid solution of a definite concentration. To this were added 20 Cc. of chloroform or ether and the mixture was shaken in a Jena Erlenmeyer flask for two hours and a half, at a temperature of 25°. The shaking was carried out in a water thermostat, accurate to within a tenth of a degree. The time of shaking was chosen after experiments were carried out to determine the time required for the reaction to come to equilibrium. It was found that in the case of strychnine tartrate only half this time was required. When that time had elapsed, the flasks were removed, the layers at once separated, and the chloroform or ether layer put in a small separatory funnel. After standing for about 10 minutes in order to make a clear separation, 10 Cc. of the chloroform solution were measured into a porcelain casserole, and the chloroform evaporated on a steam-bath. The residue was taken up in 10 Cc. of $\frac{N}{50}$ sulphuric acid, and the excess acid titrated back with standard $\frac{N}{50}$ potassium hydroxide. Such indicators were used as would give the most accurate results for the individual alkaloids. The selection of indicator was made after reference to Kippenberger's article. The value obtained in this way gave the amount of free alkaloid present in the residue. The neutral solution was made alkaline and extracted with chloroform. After separation, the solvent was evaporated and the residue again taken up in standard acid and titrated back with standard alkali. This gave the value for the total alkaloid. By subtracting the first value from the second, the amount of alkaloid present, combined with acid in the form of salt, was obtained.

With morphine, a slightly different procedure was carried out. In determining the amount of total alkaloid, the neutral solution after the first titration was made alkaline with ammonium hydroxide, since sodium and potassium hydroxide form salts with morphine which are soluble in alkaline solution. The alkaline solution was then extracted with amyl alcohol, until it showed the absence of alkaloid, amyl alcohol being the best solvent for morphine which will answer the purpose.

The solutions of the neutral salts were of the following acid strengths: Neutral, $\frac{N}{8}$, $\frac{N}{4}$, $\frac{N}{2}$. The equilibrium conditions were determined for the tartrate salts of the alkaloids aconitine, atropine, cinchonidine, cinchonine, cocaine, codeine, quinine, morphine, strychnine and veratrine, in tartaric acid solutions. The equilibrium conditions for the solutions of alkaloidal sulphates in sulphuric acid and hydrochlorides in hydrochloric acid were worked out with the idea of supplementing and adding to those values obtained by Kippenberger and Simmer. Table IX gives the results of the extraction of the salt solution by chloroform, and Table X, the values obtained by the extraction with ether.

2. Conditions at equilibrium in systems in which the alkaloid is being removed from its chloroform solution by an acid.

TABLE IX.

Alkaloid.	Acid.	Strength.	Grammes alkaloid in 20 Cc. chloroform. Total.	Free.	Salt.	Indicator.
Strychnine	HTr	N/2	0	0	0	Azolitmin
	HTr	N/4	0	0	0	Azolitmin
	HTr	N/8	0	0	0	Azolitmin
	HTr	Neut.	0.0120	0.0104	0.0016	Azolitmin
	Sulph.	N/2	0	0	0	Azolitmin
	Sulph.	N/4	0	0	0	Azolitmin
	Sulph.	N/8	0	0	0	Azolitmin
	Sulph.	N/50	0	0	0	Azolitmin
	Sulph.	Neut.	0.0127	0.0127	0	Azolitmin
	HCl	N/2	0.0522	0	0.0522	Azolitmin
	HCl	N/4	0.0424	0	0.0424	Azolitmin
	HCl	N/8	0.0394	0	0.0394	Azolitmin
		Neut.	0.0085	0.0081	0.0005	Azolitmin
Brucine	HTr	N/2	0	0	0	Azolitmin
	HTr	N/4	0	0	0	Azolitmin
	HTr	N/8	0.0026	0.0026	0	Azolitmin
	HTr	Neut.	0.0076	0.0076	0	Azolitmin
	Sulph.	N/2	0	0	0	Azolitmin
	Sulph.	N/4	0	0	0	Azolitmin
	Sulph.	N/8	0	0	0	Azolitmin
	Sulph.	Neut.	0.0143	0.0143	0	Azolitmin
Cinchonidine	HTr	N/2	0.0012	0.0012	0	Azolitmin
	HTr	N/4	0.0024	0.0024	0	Azolitmin
	HTr	N/8	0.0018	0.0018	0	Azolitmin
	HTr	Neut.	0.0024	0.0024	0	Azolitmin
	Sulph.	N/2	0	0	0	Azolitmin
	Sulph.	N/4	0	0	0	Azolitmin
	Sulph.	N/8	0	0	0	Azolitmin
	Sulph.	Neut.	0.0086	0.0086	0	Azolitmin
Cinchonine	HTr	N/2	0	0	0	Azolitmin
	HTr	N/4	0	0	0	Azolitmin
	HTr	N/8	0	0	0	Azolitmin
	HTr	Neut.	0.0016	0	0.0016	Azolitmin
Caffeine	Sulph.	N/2	0.1928	0.1928	0	weight of residue
	Sulph.	N/4	0.1930	0.1930	0	weight of residue
	Sulph.	N/8	0.1300	0.1300	0	weight of residue
	Sulph.	Neut.	0.1032	0.1032	0	weight of residue
Cocaine	HCl	N/2	0	0	0	Iodeosin
	HCl	N/4	0	0	0	Iodeosin
	HCl	N/8	0.0432	0.0432	0	Iodeosin
	HCl	Neut.	0.0432	0	0.0432	Iodeosin
Codeine	HTr	N/2	0	0	0	Azolitmin
	HTr	N/4	0	0	0	Azolitmin
	HTr	N/8	0.0018	0.0018	0	Azolitmin
	HTr	Neut.	0.0046	0.0046	0	Azolitmin
Quinine	HTr	N/2	0.0014	0	0.0014	Azolitmin
	HTr	N/4	0.0028	0.0014	0.0014	Azolitmin
	HTr	N/8	0.0018	0.0014	0.0014	Azolitmin
	Neutral salt but slightly soluble in water.					
	Sulph.	N/2	0	0	0	Azolitmin
	Sulph.	N/4	0	0	0	Azolitmin
	Sulph.	N/8	0	0	0	Azolitmin
	Sulph.	Neut.	0	0	0	Azolitmin
Aconitine	HTr	N/2	0	0	0	Cochineal
	HTr	N/4	0.0537	0	0.0537	Cochineal
	HTr	N/8	0.0099	0	0.0099	Cochineal
	HTr	Neut.	0.0236	0.0136	0.0099	Cochineal
Atropine	HTr	N/2	0	0	0	Cochineal
	HTr	N/4	0.0036	0.0036	0	Cochineal
	HTr	N/8	0.0038	0.0010	0.0028	Cochineal
	HTr	Neut.	0.0018	0.0018	0	Cochineal
Morphine	HTr	N/2	0	0	0	Cochineal
	HTr	N/4	0	0	0	Cochineal
	HTr	N/8	0	0	0	Cochineal
	HTr	Neut.	0	0	0	Cochineal
Veratrine	HTr	N/2	0.0049	0.0049	0	Cochineal
	HTr	N/4	0.0116	0.0116	0	Cochineal
	HTr	N/8	0.0112	0.0112	0	Cochineal
	HTr	Neut.	0.0294	0.0294	0	Cochineal

TABLE X[1].

Alkaloid.	Acid.	Strength.	Grammes alkaloid in 20 Cc. ether. Total.	Free.	Salt.	Indicator.
Strychnine	HTr	N/2	0	0	0	Azolitmin
	HTr	N/4	0	0	0	Azolitmin
	HTr	N/8	0	0	0	Azolitmin
	HTr	Neut.	0	0	0	Azolitmin
	Sulph.	N/2	0	0	0	Azolitmin
	Sulph.	N/4	0	0	0	Azolitmin
	Sulph.	N/8	0	0	0	Azolitmin
	Sulph.	Neut.	0.0027	0.8027	0.8027	Azolitmin
Brucine	HTr	N/2	0	0	0	Azolitmin
	HTr	N/4	0	0	0	Azolitmin
	HTr	N/8	0.0040	?	?	Azolitmin
	HTr	Neut.	0.0032	0.0032	0	Azolitmin
	Sulph.	N/2	0	0	0	Azolitmin
	Sulph.	N/4	0	0	0	Azolitmin
	Sulph.	N/8	0	0	0	Azolitmin
	Sulph.	Neut.	0	0	0	Azolitmin
Cinchonidine	HTr	N/2	0.0018	?	?	Azolitmin
	HTr	N/4	0.0018	?	?	Azolitmin
	HTr	N/8	0	0	0	Azolitmin
	HTr	Neut.	0.0024	0.0012	0.0012	Azolitmin
	Sulph.	N/2	0	0	0	Azolitmin
	Sulph.	N/4	0	0	0	Azolitmin
	Sulph.	N/8	0	0	0	Azolitmin
	Sulph.	Neut.	0.0040	0.0040	0	Azolitmin
Cinchonine	HTr	N/2	0	0	0	Azolitmin
	HTr	N/4	0	0	0	Azolitmin
	HTr	N/8	0.0014	?	?	Azolitmin
	HTr	Neut.	0.0023	0.0023	0	Azolitmin
Codeine	HTr	N/2	0	0	0	Azolitmin
	HTr	N/4	0	0	0	Azolitmin
	HTr	N/8	0	0	0	Azolitmin
	HTr	Neut.	0	0	0	Azolitmin
	Sulph.	N/2	0	0	0	Azolitmin
	Sulph.	N/4	0	0	0	Azolitmin
	Sulph.	N/8	0.0023	0	0.0023	Azolitmin
	Sulph.	Neut.	0	0	0	Azolitmin
Aconitine	HTr	N/2	0	0	0	Cochineal
	HTr	N/4	0	0	0	Cochineal
	HTr	N/8	0.0052	?	?	Cochineal
	HTr	Neut.	0.0060	0	0.0060	Cochineal
Atropine	HTr	N/2	0	0	0	Cochineal
	HTr	N/4	0.0011	?	?	Cochineal
	HTr	N/8	0.0014	?	?	Cochineal
	HTr	Neut.	0.0021	0	0.0021	Cochineal
Morphine	HTr	N/2	0	0	0	Cochineal
	HTr	N/4	0	0	0	Cochineal
	HTr	N/8	0	0	0	Cochineal
	HTr	Neut.	0	0	0	Cochineal
	Sulph.	N/2	0	0	0	Cochineal
	Sulph.	N/4	0	0	0	Cochineal
	Sulph.	N/8	0.0011	0.0011	0	Cochineal
	Sulph.	Neut.	0.0019	0.0019	0	Cochineal
Quinine	HTr	N/2	0	0	0	Azolitmin
	HTr	N/4	0	0	0	Azolitmin
	HTr	N/8	0.0014	?	?	Azolitmin
	Sulph.	N/2	0	0	0	Azolitmin
	Sulph.	N/4	0	0	0	Azolitmin
	Sulph.	N/8	0	0	0	Azolitmin
	Sulph.	Neut.	0	0	0	Azolitmin
Veratrine	HTr	N/2	0	0	0	Cochineal
	HTr	N/4	0	0	0	Cochineal
	HTr	N/8	0	0	0	Cochineal
	HTr	Neut.	0.0024	0.0024	0	Cochineal

[1] Owing to the solubility of tartaric acid in ether, it is impossible to say whether the salt is present in the ether in the free state or as salt, in the extraction from acid solution.

0.2 Gm. of the alkaloid were dissolved in 20 Cc. of chloroform and 25 Cc. of the required concentration acid added. The mixture was shaken for two hours and a half, in the same manner as was the previous case, at 25°. After separation of the two layers, the amount of alkaloid and alkaloidal salt in the chloroform layer was determined. The results are tabulated in Table XI. Owing to the insolubility of some of the alkaloids in ether, values were not always obtained for the use of this solvent. The chloroform solutions of the alkaloids were shaken out with sulphuric, hydrochloric and tartaric acids of the concentrations, $\frac{N}{2}$, $\frac{N}{4}$, $\frac{N}{8}$. In the case of strychnine, even more dilute acid solutions were used. In those cases where the salt formed is but slowly soluble in the acids, experiments were made to determine how many shakings would more quickly dissolve the salt, and what strength acid would be best.

TABLE XI.

Alkaloid.	Nature, volume, acid.	Cc.	Strength.	Grammes alkaloid in 20 Cc. chloroform. Total.	Free.	Salt.	Indicator.
Aconitine	HTr	25	N/2	0	0	0	Cochineal
	HTr	50	N/4	0	0	0	Cochineal
	HTr	50	N/8	0	0	0	Cochineal
	HCl	25	N/2	0.0342	0	0.0342	Cochineal
	HCl	25	N/4	0.0257	0	0.0257	Cochineal
	HCl	25	N/8	0.0146	0	0.0146	Cochineal
Atropine	HTr	25	N/4	0.0146	0.0010	0	Cochineal
	HTr	25	N/8	0.0010	0.0010	0	Cochineal
Brucine	HTr	25	N/2	0	0	0	Azolitmin
	HTr	25	N/4	0	0	0	Azolitmin
	HTr	25	N/8	0.0014	0.0014	0	Azolitmin
	HTr	35	N/8	0	0	0	Azolitmin
	Sulph.	25	N/2	0	0	0	Azolitmin
	Sulph.	25	N/4	0.0008	0.0008	0	Azolitmin
	Sulph.	25	N/8	0.0012	0.0012	0	Azolitmin
	HCl	25	N/2	0.0768	0	0.0768	Azolitmin
	HCl	25	N/4	0.0583	0	0.0583	Azolitmin
	HCl	25	N/8	0.0445	0	0.0445	Azolitmin
Cinchonidine	HTr	25	N/2	0	0	0	Azolitmin
	HTr	50	N/4	0	0	0	Azolitmin
	HTr	50	N/8	0	0	0	Azolitmin
	Sulph.	25	N/2	0	0	0	Azolitmin
	Sulph.	25	N/4	0	0	0	Azolitmin
	Sulph.	25	N/8	0.0012	0.0012	0	Azolitmin
	HCl	25	N/2	0	0	0	Azolitmin
	HCl	25	N/4	0	0	0	Azolitmin
	HCl	25	N/8	0	0	0	Azolitmin
Cinchonine	HTr	25	N/2	0	0	0	Azolitmin
	HTr	25	N/4	0	0	0	Azolitmin
	HTr	25	N/8	0	0	0	Azolitmin
	Sulph.	25	N/2	0	0	0	Azolitmin
	Sulph.	25	N/4	0	0	0	Azolitmin
	Sulph.	25	N/8	0.0011	0.0011	0	Azolitmin
	HCl	25	N/2	0	0	0	Azolitmin
	HCl	25	N/4	0	0	0	Azolitmin
	HCl	25	N/8	0	0	0	Azolitmin
Cocaine	HTr	25	N/2	0	0	0	Cochineal
	HTr	25	N/4	0	0	0	Cochineal
	HTr	25	N/8	0.0017	0.0017	0	Cochineal
	Sulph.	25	N/2	0	0	0	Cochineal
	Sulph.	25	N/4	0	0	0	Cochineal
	Sulph.	25	N/8	0	0	0	Cochineal
	HCl	25	N/2	0	0	0	Cochineal
	HCl	25	N/4	0	0	0	Cochineal
	HCl	25	N/8	0	0	0	Cochineal

TABLE XI.—*Continued.*

Alkaloid.	Nature, volume, acid.	Cc.	Strength.	Grammes alkaloid in 20 Cc. chloroform. Total.	Free.	Salt.	Indicator.
Codeine	HTr	25	N/2	0	0	0	Azolitmin
	HTr	25	N/4	0	0	0	Azolitmin
	HTr	25	N/8	0	0	0	Azolitmin
	Sulph.	25	N/2	0	0	0	Azolitmin
	Sulph.	25	N/4	0	0	0	Azolitmin
	Sulph.	25	N/8	0	0	0	Azolitmin
	HCl	25	N/2	0	0	0	Azolitmin
	HCl	25	N/4	0	0	0	Azolitmin
	HCl	25	N/8	0	0	0	Azolitmin
Quinine	HTr	25	N/2	0	0	0	Azolitmin
	HTr	25	N/4	0	0	0	Azolitmin
	HTr	25	N/8	0	0	0	Azolitmin
	Sulph.	25	N/2	0	0	0	Azolitmin
	Sulph.	25	N/4	0	0	0	Azolitmin
	Sulph.	25	N/8	0	0	0	Azolitmin
	HCl	25	N/2	0	0	0	Azolitmin
	HCl	25	N/4	0	0	0	Azolitmin
	HCl	25	N/8	0	0	0	Azolitmin
Strychnine	HTr	50	4N	0	0	0	Azolitmin
	HTr	100	2N	0	0	0	Azolitmin
	HTr	100	N	0.0011	0	0.0011	Azolitmin
	HTr	100	N/2	0.0011	0	0.0011	Azolitmin
	HTr	95	N/4	0.0011	0	0.0011	Azolitmin
	HTr	75	N/8	0.0011	0	0.0011	Azolitmin
	HTr	75	N/12	0.0029	0	0.0029	Azolitmin
	HTr	25	N/25	0.0125	0	0.0125	Azolitmin
	HCl	25	N/2	0.0202	0	0.0202	Azolitmin
	HCl	25	N/4	0.0250	0	0.0250	Azolitmin
	HCl	25	N/8	0.0202	0	0.0202	Azolitmin
Veratrine	HTr	25	N/2	0.0020	0.0020	0.0020	Cochineal
	HTr	25	N/4	0.0040	0.0040	0	Cochineal
	HTr	25	N/8	0	0	0	Cochineal
	Sulph.	25	N/2	0	0	0	Cochineal
	Sulph.	25	N/4	0	0	0	Cochineal
	Sulph.	25	N/8	0	0	0	Cochineal
	HCl	25	N/2	0.0740	0	0.0740	Cochineal
	HCl	25	N/4	0.0516	0	0.0516	Cochineal
	HCl	25	N/8	0.0426	0	0.0426	Cochineal

(*c*) Calculation of the *extraction factors* under the various equilibrium conditions examined, as well as those reported in the literature:

The *extraction factor* is simply the ratio of the amount of alkaloid found in the layer of the added solvent to the amount originally present in the first solution, regardless of the volumes of the two solutions. This gives an excellent idea of the efficiency of the different sets of extraction conditions.

Table XII contains the data and values for the extraction factors for the alkaloidal tartrates between tartaric acid and chloroform. In Table XIII will be found similar values where ether has been used as the solvent. The extraction factors for the sulphates between sulphuric acid and chloroform and of the hydrochlorides between hydrochloric acid and chloroform are found in Tables XIV and XV, respectively. Table XVI contains the values, using ether for the solvent, for the sulphates.

The extraction factors for the extraction of the alkaloids from their chloroform solutions, by tartaric, sulphuric and hydrochloric acids, will be found in Table XVII.

TABLE XII.

Alkaloid.	Acid.	Strength.	Chloroform. Volume.	Chloroform. Alkaloid.	Acid volume.	Original total alkaloid.	Factor.
Strychnine	HTr	N/2	20	0	25	0.1650	0
	HTr	N/4	20	0	25	0.1650	0
	HTr	N/8	20	0.0104	25	0.1650	0.0634
	HTr	Neut.	20	0.0126	25	0.1650	0.0768
Brucine	HTr	N/2	20	0	25	0.1680	0
	HTr	N/4	20	0	25	0.1680	0
	HTr	N/8	20	0.0026	25	0.1680	0.0154
	HTr	Neut.	20	0.0076	25	0.1680	0.0453
Cinchonidine	HTr	N/2	20	0.0012	25	0.1595	0.0076
	HTr	N/4	20	0.0024	25	0.1595	0.0153
	HTr	N/8	20	0.0018	25	0.1595	0.0114
	HTr	Neut.	20	0.0024	25	0.1595	0.0153
Cinchonine	HTr	N/2	20	0	25	0.1595	0
	HTr	N/4	20	0	25	0.1595	0
	HTr	N/8	20	0	25	0.1595	0
	HTr	Neut.	20	0.0016	25	0.1595	0.0100
Quinine	HTr	N/2	20	0.0014	25	0.1625	0.0086
	HTr	N/4	20	0.0028	25	0.1625	0.0172
	HTr	N/8	20	0.0028	25	0.1625	0.0172
Aconitine	HTr	N/2	20	0	25	0.1930	0
	HTr	N/4	20	0.0053	25	0.1930	0.0274
	HTr	N/8	20	0.0099	25	0.1930	0.0512
	HTr	Neut.	20	0.0360	25	0.1930	0.1240
Atropine	HTr	N/2	20	0	25	0.1585	0
	HTr	N/4	20	0.0036	25	0.1585	0.0217
	HTr	N/8	20	0.0039	25	0.1585	0.0245
	HTr	Neut.	20	0.0018	25	0.1585	0.0108
Codeine	HTr	N/2	20	0	25	0.1600	0
	HTr	N/4	20	0	25	0.1600	0
	HTr	N/8	20	0.0018	25	0.1600	0.0116
	HTr	Neut.	20	0.0046	25	0.1600	0.0286
Morphine	HTr	N/2	20	0	25	0.1585	0
	HTr	N/4	20	0	25	0.1585	0
	HTr	N/8	20	0	25	0.1585	0
	HTr	Neut.	20	0	25	0.1585	0
Veratrine	HTr	N/2	20	0.0049	25	0.1775	0.0276
	HTr	N/4	20	0.0116	25	0.1775	0.0645
	HTr	N/8	20	0.0112	25	0.1775	0.0630
	HTr	Neut.	20	0.0294	25	0.1775	0.1655

TABLE XIII.

Alkaloid.	Acid.	Strength.	Chloroform. Volume.	Chloroform. Alkaloid.	Acid volume.	Original total alkaloid.	Factor.
Strychnine	HTr	N/2	20	0	25	0.1640	0
	HTr	N/4	20	0	25	0.1640	0
	HTr	N/8	20	0	25	0.1640	0
	HTr	Neut.	20	0	25	0.1640	0
Brucine	HTr	N/2	20	0	25	0.1680	0
	HTr	N/4	20	0	25	0.1680	0
	HTr	N/8	20	0.0040	25	0.1680	0.0238
	HTr	Neut.	20	0.0032	25	0.1680	0.0191
Morphine	HTr	N/2	20	0	25	0.1585	0
	HTr	N/4	20	0	25	0.1585	0
	HTr	N/8	20	0	25	0.1585	0
	HTr	Neut.	20	0	25	0.1585	0
Cinchonidine	HTr	N/2	20	0.0018	25	0.1595	0.0114
	HTr	N/4	20	0.0018	25	0.1595	0.0114
	HTr	N/8	20	0	25	0.1595	0
	HTr	Neut.	20	0.0024	25	0.1595	0.0153
Cinchonine	HTr	N/4	20	0	25	0.1595	0
	HTr	N/8	20	0	25	0.1595	0
	HTr	N/8	20	0.0014	25	0.1595	0.0087
	HTr	Neut.	20	0.0023	25	0.1595	0.0144

TABLE XIII.—*Continued.*

Alkaloid	Acid.	Strength.	Chloroform. Volume.	Chloroform. Alkaloid.	Acid volume.	Original total alkaloid.	Factor.
Quinine	HTr	N/2	20	0	25	0.1625	0
	HTr	N/4	20	0	25	0.1625	0
	HTr	N/8	20	0.0014	25	0.1625	0.0086
Codeine	HTr	N/2	20	0	25	0.1600	0
	HTr	N/4	20	0	25	0.1600	0
	HTr	N/8	20	0	25	0.1600	0
	HTr	Neut.	20	0	25	0.1600	0
Aconitine	HTr	N/2	20	0	25	0.1930	0
	HTr	N/4	20	0	25	0.1930	0
	HTr	N/8	20	0.0052	25	0.1930	0.0269
	HTr	Neut.	20	0.0060	25	0.1930	0.0310
Atropine	HTr	N/2	20	0	25	0.1585	0
	HTr	N/4	20	0.0011	25	0.1585	0.0069
	HTr	N/8	20	0.0014	25	0.1585	0.0088
	HTr	Neut.	20	0.0021	25	0.1585	0.0132
Veratrine	HTr	N/2	20	0	25	0.1775	0
	HTr	N/4	20	0	25	0.1775	0
	HTr	N/8	20	0	25	0.1775	0
	HTr	Neut.	20	0.0024	25	0.1775	0.0135

TABLE XIV.

Alkaloid.	Strength.	Chloroform volume.	Alkaloid.	Acid volume.	Total alkaloid.	Extraction factor.	References.
Strychnine	N/2	20	0	25	0.1745	0	Authors
	N/4	20	0	25	0.1745	0	Authors
	N/8	20	0	25	0.1745	0	Authors
	N/50	20	0	25	0.1745	0	Authors
	Neut.	20	0.0127	25	0.1745	0.0727	Authors
	.17N	50	Traces	70	0.2000	0	Kippenberger
	1 percent.	50?	Traces	50	0.2610	0	Simmer
	Neut.	50?	Traces	50	0.2610	0	Simmer
Brucine	N/2	20	0	25	0.1780	0	Authors
	N/4	20	0	25	0.1780	0	Authors
	N/8	20	0	25	0.1780	0	Authors
	Neut.	20	0.0143	25	0.1780	0.0803	Authors
	.17N	50	0.0020	70	0.2000	0.0100	Kippenberger
Cinchonidine	N/2	20	0	25	0.1715	0	Authors
	N/4	20	0	25	0.1715	0	Authors
	N/8	20	0	25	0.1715	0	Authors
	Neut.	20	0.0086	25	0.1715	0.0503	Authors
Quinine	N/2	20	0	25	0.1740	0	Authors
	N/4	20	0	25	0.1740	0	Authors
	N/8	20	0	25	0.1740	0	Authors
	Neut.	20	0	25	0.1740	0	Authors
	.034N	50	0	70	0.2000	0	Kippenberger
Atropine	.034N	50	0	70	0.2000	0	Kippenberger
	Neut.	50	0.0010	70	0.2000	0.0050	Kippenberger
Morphine	.034N	50	0	70	0.2000	0	Kippenberger
Aconitine	.255N	50	Traces	70	0.2000	0	Kippenberger
	.085N	50	0.0064	70	0.2000	0.0320	Kippenberger
	.017N	50	0.0130	70	0.2000	0.0650	Kippenberger
Veratrine	.017N	50	Traces	70	0.2000	0	Kippenberger
	N/40	50?	Traces	50	0.2150	0	Simmer
	Neut.	50?	0.0374	50	0.2150	0.1780	Simmer
Codeine	.034N	50	0	70	0.2000	0	Kippenberger
	N/49	50?	Traces	50	0.2470	0	Simmer
	Neut.	50?	0.0276	50	0.2470	0.1116	Simmer
Cocaine	.255N	50	0	70	0.2000	0	Kippenberger
	.017N	50	Traces	70	0.2000	0	Kippenberger
	Neut.	50?	0.0143	50	0.2640	0.0540	Simmer

TABLE XV.

Acid—Hydrochloric Acid:

Alkaloid.	Strength.	Chloroform volume.	Alkaloid.	Acid volume.	Total alkaloid.	Extraction factor.	References.
Strychnine.....	N/2	20	0.0522	25	0.080	0.2895	Authors
	N/4	20	0.0424	25	0.080	0.2360	Authors
	N/8	20	0.0394	25	0.080	0.2182	Authors
	Neut.	20	0.0085	25	0.080	0.0472	Authors
	6.75N	50	0.0920	70	0.200	0.4600	Kippenberger
	6.85N	50?	0.0233	50	0.2377	0.1020	Simmer
	2.74N	50?	0.0559	50	0.2377	0.2360	Simmer
	.274N	50?	0.0250	50	0.2377	0.1050	Simmer
	.027N	50?	0.0083	50	0.2377	0.0340	Simmer
	Neut.	50?	0.0158	50	0.2377	0.0665	Simmer
Brucine.....	.075N	50	0.0898	70	0.2000	0.4490	Kippenberger
Cocaine.....	N/2	20	0	25	0.1790	0	Authors
	N/4	20	0	25	0.1790	0	Authors
	N/8	20	0.0432	25	0.1790	0.2420	Authors
	Neut.	20	0.0432	25	0.1790	0.2420	Authors
	2.74N	50?	0.0075	50	0.2240	0.0335	Simmer
	.274N	50?	0.0045	50	0.2240	0.0210	Simmer
	.027N	50?	0.0037	50	0.2240	0.0165	Simmer
	Neut.	50?	0.0490	50	0.2240	0.4900	Simmer
	.017N	150	0.0021	70	0.2000	0.0110	Kippenberger
Atropine.....	.075N	50	0.0014	70	0.2000	0.0070	Kippenberger
	2.74N	50?	0.0028	50	0.2250	0.0124	Simmer
	.027N	50?	0	50	0.2250	0	Simmer
	Neut.	50?	0	50	0.2250	0	Simmer
Morphine.....	.075N	50	0	70	0.2000	0	Kippenberger
	1.37N	50?	0	50	0.2470	0	Simmer
	.027N	50?	0	50	0.2470	0	Simmer
	Neut.	50?	0.0045	50	0.2470	0.0182	Simmer
Aconitine.....	.030N	50	0.0971	70	0.2000	0.4850	Kippenberger
Veratrine.....	.075N	50	0.0807	70	0.2000	0.4035	Kippenberger
	2.74N	50?	0.1248	50	0.2110	0.5920	Simmer
	.027N	50?	0.0327	50	0.2110	0.1550	Simmer
	Neut.	50?	0.0530	50	0.2110	0.2520	Simmer
Codeine.....	.030N	50	Traces	70	0.2000	0	Kippenberger
	2.74N	50?	0.0079	50	0.2340	0.0338	Simmer
	.027N	50?	0.0015	50	0.2340	0.0064	Simmer
	Neut.	50?	0.0371	50	0.2340	0.0158	Simmer

TABLE XVI.

Acid—Sulphuric Acid:

Alkaloid.	Acid, strength.	Ether. Volume.	Ether. Alkaloid.	Acid volume.	Original total alkaloid.	Extraction factor.
Strychnine.....	N/2	20	0	25	0.1745	0
	N/4	20	0	25	0.1745	0
	N/8	20	0	25	0.1745	0
	Neut.	20	0.0027	25	0.1745	0.0055
Brucine.....	N/2	20	0	25	0.1780	0
	N/4	20	0	25	0.1780	0
	N/8	20	0	25	0.1780	0
	Neut.	20	0	25	0.1780	0
Morphine.....	N/2	20	0	25	0.1730	0
	N/2	20	0	25	0.1730	0
	N/8	20	0.0011	25	0.1730	0.0063
	Neut.	20	0.0019	25	0.1730	0.0010
Cinchonidine.....	N/2	20	0	25	0.1715	0
	N/4	20	0	25	0.1715	0
	N/8	20	0	25	0.1715	0
	Neut.	20	0.0040	25	0.1715	0.0237
Quinine.....	N/2	20	0	25	0.1740	0
	N/4	20	0	25	0.1740	0
	N/8	20	0	25	0.1740	0
	Neut.	20	0	25	0.1740	0
Codeine.....	N/2	20	0	25	0.1720	0
	N/4	20	0	25	0.1720	0
	N/8	20	0.0024	25	0.1720	0.0139
	Neut.	20	0	25	0.1720	0

TABLE XVII.

Alkaloid.	Acid.	Chloroform. Strength.	Chloroform. Volume.	Original alkaloid.	Acid volume.	Weight in acid alkaloid.	Extraction factor.
Aconitine	HTr	N/2	20	0.200	25	0.200	1.00
	HTr	N/4	20	0.200	50	0.200	1.00
	HTr	N/8	20	0.200	50	0.200	1.00
	HCl	N/2	20	0.200	25	0.165	0.830
	HCl	N/4	20	0.200	25	0.174	0.872
	HCl	N/8	20	0.200	25	0.186	0.930
Atropine	HTr	N/4	20	0.150	25	0.149	0.994
	HTr	N/8	20	0.200	25	0.199	0.996
Brucine	HTr	N/2	20	0.200	25	0.200	1.00
	HTr	N/4	20	0.200	25	0.200	1.00
	HTr	N/8	20	0.200	25	0.192	0.964
	HTr	N/8	20	0.200	25	0.200	1.00
	Sulph.	N/2	20	0.200	25	0.200	1.00
	Sulph.	N/4	20	0.200	25	0.199	0.996
	Sulph.	N/8	20	0.200	25	0.198	0.994
	HCl	N/2	20	0.200	25	0.1232	0.617
	HCl	N/4	20	0.200	25	0.1417	0.7088
	HCl	N/8	20	0.200	25	0.1555	0.777
Cinchonidine	HTr	N/2	20	0.200	25	0.200	1.00
	HTr	N/4	20	0.200	50	0.200	1.00
	HTr	N/8	20	0.200	50	0.200	1.00
	Sulph.	N/2	20	0.200	25	0.200	1.00
	Sulph.	N/4	20	0.200	25	0.200	1.00
	Sulph.	N/8	20	0.200	25	0.1988	0.996
	HCl	N/2	20	0.200	25	0.200	1.00
	HCl	N/4	20	0.200	25	0.200	1.00
	HCl	N/8	20	0.200	25	0.200	1.00
Cinchonine	HTr	N/2	20	0.200	25	0.200	1.00
	HTr	N/4	20	0.200	25	0.200	1.00
	HTr	N/8	20	0.200	25	0.200	1.00
	Sulph.	N/2	20	0.200	25	0.200	1.00
	Sulph.	N/4	20	0.200	25	0.200	1.00
	Sulph.	N/8	20	0.200	25	0.1998	0.998
	HCl	N/2	20	0.200	25	0.200	1.00
	HCl	N/4	20	0.200	25	0.200	1.00
	HCl	N/8	20	0.200	25	0.200	1.00
Cocaine	HTr	N/2	20	0.200	25	0.200	1.00
	HTr	N/4	20	0.200	25	0.200	1.00
	HTr	N/8	20	0.200	25	0.198	0.990
	Sulph.	N/2	20	0.200	25	0.200	1.00
	Sulph.	N/4	20	0.200	25	0.200	1.00
	Sulph.	N/8	20	0.200	25	0.200	1.00
	HCl	N/2	20	0.200	25	0.200	1.00
	HCl	N/4	20	0.200	25	0.200	1.00
	HCl	N/8	20	0.200	25	0.200	1.00
Codeine	HTr	N/2	20	0.200	25	0.200	1.00
	HTr	N/4	20	0.200	25	0.200	1.00
	HTr	N/8	20	0.200	25	0.200	1.00
	Sulph.	N/2	20	0.200	25	0.200	1.00
	Sulph.	N/4	20	0.200	25	0.200	1.00
	Sulph.	N/8	20	0.200	25	0.200	1.00
	HCl	N/2	20	0.200	25	0.200	1.00
	HCl	N/4	20	0.200	25	0.200	1.00
	HCl	N/8	20	0.200	25	0.200	1.00
Quinine	HTr	N/2	20	0.200	25	0.200	1.00
	HTr	N/4	20	0.200	25	0.200	1.00
	HTr	N/8	20	0.200	25	0.200	1.00
	Sulph.	N/2	20	0.200	25	0.200	1.00
	Sulph.	N/4	20	0.200	25	0.200	1.00
	Sulph.	N/8	20	0.200	25	0.200	1.00
	HCl	N/2	20	0.200	25	0.200	1.00
	HCl	N/4	20	0.200	25	0.200	1.00
	HCl	N/8	20	0.200	25	0.200	1.00

TABLE XVII.—*Continued.*

Alkaloid.	Acid.	Chloroform. Strength.	Chloroform. Volume.	Original alkaloid.	Acid volume.	Weight in acid alkaloid.	Extraction factor.
Strychnine.....	HTr	4N	20	0.200	50	0.200	1.00
	HTr	2N	20	0.200	100	0.200	1.00
	HTr	N	20	0.200	100	0.198	0.996
	HTr	N/2	20	0.200	100	0.198	0.996
	HTr	N/4	20	0.200	95	0.198	0.996
	HTr	N/8	20	0.200	75	0.198	0.996
	HTr	N/12	20	0.200	75	0.197	0.986
	HTr	N/25	20	0.200	25	0.187	0.938
	HCl	N/2	20	0.200	25	0.179	0.900
	HCl	N/4	20	0.200	25	0.175	0.875
	HCl	N/8	20	0.200	25	0.179	0.899
Veratrine.....	HTr	N/2	20	0.200	25	0.198	0.990
	HTr	N/4	20	0.200	25	0.196	0.990
	HTr	N/8	20	0.200	25	0.200	1.00
	Sulph.	N/2	20	0.200	25	0.200	1.00
	Sulph.	N/4	20	0.200	25	0.200	1.00
	Sulph.	N/8	20	0.200	25	0.200	1.00
	HCl	N/2	20	0.200	25	0.126	0.630
	HCl	N/4	20	0.200	25	0.148	0.742
	HCl	N/8	20	0.200	25	0.157	0.787

V. DISCUSSION OF RESULTS.

In looking over the tables, the following results will be observed:

Aconitine.—In the washing of a solution of aconitine tartrate with chloroform, it is seen that the more concentrated the acid is, the less alkaloid will be removed. Hydrolysis takes place in the neutral solution with the removal of about 11 percent of the alkaloid in the free state. Whatever alkaloid is removed from the acid solution is removed in the form of salt and not in the free state. Aconitine is also removed from solution in sulphuric acid, provided the acid is less than $\frac{N}{4}$ concentration, but in much smaller amounts than from tartaric acid. From hydrochloric acid solution the amount of alkaloid removed is in direct proportion to the strength of the acid and the alkaloid is almost entirely removed as the salt, showing that chloroform is a fairly good solvent for the hydrochlorides of aconitine.

Atropine.—The same phenomena will be observed in the cases of the sulphates and tartrates of atropine, namely, that as acidity increases, less alkaloid will be removed by ether or chloroform. With the hydrochlorides it is reversed, and as the strength of the acid increases, the amount of alkaloid removed increases, and it is removed as the salt.

Brucine.—Brucine is not removed from tartaric acid solutions of strength greater than $\frac{N}{4}$ by either chloroform or ether, although with a decrease in the concentration of the acid from that point down, there is increased hydrolytic action with the removal of the alkaloid in the uncombined state. Sulphuric acid retains the alkaloid from removal by either chloroform or ether from acid solution, and ether does not even extract any from the neutral solution. From a $\frac{N}{0.075}$ solution of the hydrochloride in hydrochloric acid, 45 percent of the alkaloid is removed by chloroform and most of it as the salt.

Cinchonidine and Cinchonine.—Cinchonidine, cinchonine, and quinine differ from the other alkaloids in that their hydrochlorides are insoluble in chloroform. Many of the hydrochlorides of the other alkaloids are soluble to a great extent in this solvent. The neutral tartrates and sulphates are hydrolyzed and the alkaloids removed by both ether and chloroform. Cinchonidine differs from cinchonine

in that the tartrates are hydrolyzed in acid solution and some of the alkaloid removed as free cinchonidine.

Quinine.—Quinine sulphate is neither hydrolyzed in neutral and acid solution nor is the salt soluble in either ether or chloroform. The neutral tartrate is only slightly soluble in water but the $\frac{N}{8}$ acid solution is hydrolyzed to a slight extent, giving up quinine in both the free and combined condition to chloroform and in the free state to ether.

Morphine.—Neither chloroform nor ether remove morphine from the neutral or acid solution of the tartrate. The neutral sulphate is slightly hydrolyzed and some free morphine found in the ether.

Strychnine.—Hydrolytic action takes place in the $\frac{N}{8}$ tartaric acid and neutral solution of the strychnine tartrate and some alkaloid is removed by the chloroform in the free state. Increase in acidity with both the sulphates and tartrates causes a decrease in the amount of alkaloid removed, the reverse being true in the case of the hydrochlorides.

Veratrine.—Veratrine is removed in appreciable amounts from the tartaric acid solution by chloroform, but only from the neutral solution by ether. Chloroform does not take up any of the alkaloid from the sulphuric acid, but appreciably lowers the concentration of the alkaloid in the hydrochloric acid solutions.

Codeine.—Neither ether nor chloroform will remove codeine from solution in $\frac{N}{2}$ or $\frac{N}{4}$ tartaric acid, but chloroform removes increasing amounts as the concentration of the acid decreases from that point on. The hydrochlorides are more soluble in chloroform the greater the concentration of the acid. Hydrolysis takes place in the neutral solutions and much codeine is removed.

In general, the following principles may be apparent in the foregoing:

1. The neutral sulphates and tartrates in aqueous solution are hydrolyzed to a certain extent with the subsequent formation of free alkaloid and acid. This alkaloid may be removed by the immiscible solvent.

2. With an increase in the acidity of the solution the hydrolytic action becomes less and the amount of alkaloid taken up in the free state decreases with the increase in acidity.

3. Many of the acid sulphates and tartrates are removed as salts to a slight degree by chloroform and ether.

4. The alkaloidal hydrochlorides tend to be quite soluble in chloroform, and in such cases the solubility increases with the acidity of the solution, in all the cases studied.

By means of this data, the following questions may be answered:

1. What conditions of acidity would completely remove the alkaloid from its chloroform solution?

2. Which solvent, chloroform or ether, can best be used for shaking out the neutral or acid solution of the alkaloidal tartrates or sulphates, without removing the alkaloid?

3. And which salts are least easily removed by chloroform or ether, and in what concentration of acid, either by hydrolysis or through the solubility of the salt itself in the immiscible solvent?

1. The best conditions of acidity for completely removing the alkaloids from the chloroform solution. Table XVIII gives the values for the extraction of 0.2 Gm. of the alkaloid from 20 Cc. of the solvent chloroform, by the different acids:

TABLE XVIII.

Alkaloid.	Acid.	Strength.	Volume.
Aconitine	HTr	N/8	2 portions of 25 Cc. each
Atropine	HTr	N/8	1 portion of 25 and 1 of 10 Cc.
Brucine	HTr	N/8	1 portion of 25 and 1 of 10 Cc.
Cinchonidine and Cinchonine	HCl	N/8	25 Cc.
	Sulph.	N/8	1 portion of 25 and 1 of 10 Cc.
Cocaine and Codeine	Sulph.	N/8	25 Cc.
	HCl	N/8	25 Cc.
Quinine	HCl	N/8	25 Cc.
	HTr	N/8	25 Cc.
	Sulph.	N/8	25 Cc.
Strychnine	HTr	N/8	3 portions of 25 Cc. each
Veratrine	HTr	N/8	25 Cc.
	Sulph.	N/8	25 Cc.

2. The best solvent for shaking out the neutral and acid solutions of the alkaloidal tartrates, without the loss of alkaloid:

TABLE XIX.

Alkaloid.	Solvent.	Strength HTr.	Percent alkaloid removed.
Aconitine	Ether	N/4	0
Atropine	Chloroform	Slightly acid	1.0
Brucine	Chloroform	N/8	1.5
Cinchonidine	Ether	Slightly acid	1.2
Cinchonine	Chloroform	N/8	0
Codeine	Ether	N/8	0
Quinine	Ether	N/8	0.8
Morphine	Either one	Slightly acid	0
Strychnine	Ether	Slightly acid	0
Veratrine	Ether	Slightly N/8	0

3. The salts that are least easily removed by chloroform or ether and the best concentration of acid:

TABLE XX.

	Chloroform.			Ether.		
Alkaloid.	Salts.	Strength acid.	Percent removed.	Salts.	Strength acid.	Percent removed.
Aconitine	Sulphate	N/4	0	Tartrate	N/4	0
	Tartrate	N/4	0			
Atropine	HCl	0.02N	0	Sulphate	N/10	0
Brucine	Sulphate	N/8	0	Sulphate	N/10	0
Cinchonine	Tartrate	N/8	0	Tartrate	N/8	0.8
Cinchonidine	Sulphate	N/8	0	Tartrate	N/8	0
Codeine	Sulphate	N/50	0	Sulphate	N/10	0
Quinine	Sulphate	N/50	0	Sulphate	N/10	0
Morphine	Sulphate	N/50	0	Tartrate	N/8	0
Strychnine	Sulphate	N/50	0	Tartrate	N/8	0
Veratrine	Sulphate	N/50	0	Tartrate	N/8	0

In addition, calculations may be made which will tell how many shakings from chloroform solution need be made by an acid to completely remove the alkaloid from the chloroform solution. If 94 percent of the alkaloid is removed in the first shaking with 25 Cc. of acid, the second extraction will remove 94 percent of the 6 percent left, or 5.86 percent. Thus these two extractions will remove 99.86 percent of the alkaloid. A third extraction will take away 94 percent of the remaining 0.14 percent, or 0.131 percent, so the three extractions with the acid will make practically a complete removal.

Table XXI shows the number of shakings necessary to remove 0.2 Gm. of alkaloid from 20 Cc. of a chloroform solution.

TABLE XXI.

Alkaloid.	Acid.	Strength.	Percent alkaloid removed in first shaking.	Number of shakings for complete removal.	Total acid volume.
Aconitine	HTr	N/2	100	1	25
	HTr	N/4	100	1	25
	HTr	N/8	100	1	25
	HCl	N/2	83.0	4	100
	HCl	N/4	87.2	3	75
	HCl	N/8	93.0	3	75
Atropine	HTr	N/4	99.4	2	35
	HTr	N/8	99.6	2	25
Brucine	HTr	N/2	100	1	25
	HTr	N/4	100	1	25
	HTr	N/8	96.4	2	35
	Sulph	N/2	100	1	25
	Sulph.	N/4	99.6	2	35
	Sulph.	N/8	99.4	2	35
	HCl	N/2	61.7	6	150
	HCl	N/4	70.8	5	125
	HCl	N/8	77.7	4	100
Cinchonidine	HTr	N/2	100	1	25
	HTr	N/4	100	1	25
	HTr	N/8	100	1	25
	HCl	N/2	100	1	25
	HCl	N/4	100	1	25
	HCl	N/8	100	1	25
	Sulph.	N/2	100	1	25
	Sulph.	N/4	100	1	25
	Sulph.	N/8	99.5	1	35
Cinchonine	HTr	N/2	100	1	25
	HTr	N/4	100	1	25
	HTr	N/8	100	1	25
	HCl	N/2	100	1	25
	HCl	N/4	100	1	25
	HCl	N/8	100	1	25
	Sulph.	N/2	100	1	25
	Sulph.	N/4	100	1	25
	Sulph.	N/8	99.8	2	35
Cocaine	HTr	N/2	100	1	25
	HTr	N/4	100	1	25
	HTr	N/8	99.0	2	35
	Sulph.	N/2	100	1	25
	Sulph.	N/4	100	1	25
	Sulph.	N/8	100	1	25
	HCl	N/2	100	1	25
	HCl	N/4	100	1	25
	HCl	N/8	100	1	25
Codeine	HTr	N/2	100	1	25
	HTr	N/4	100	1	25
	HTr	N/8	100	1	25
	Sulph.	N/2	100	1	25
	Sulph.	N/4	100	1	25
	Sulph.	N/8	100	1	25
	HCl	N/2	100	1	25
	HCl	N/4	100	1	25
	HCl	N/8	100	1	25
Quinine	HTr	N/2	100	1	25
	HTr	N/4	100	1	25
	HTr	N/8	100	1	25
	Sulph.	N/2	100	1	25
	Sulph.	N/4	100	1	25
	Sulph.	N/8	100	1	25
	HCl	N/2	100	1	25
	HCl	N/4	100	1	25
	HCl	N/8	100	1	25

TABLE XXI.—*Continued.*

Alkaloid.	Acid.	Strength.	Percent alkaloid removed in first shaking.	Number of shakings for complete removal.	Total acid volume.
Strychnine.....	HTr	N	100	After 2 shakings of 25 Cc. each	
	HTr	N/2	100	After 4 shakings of 25 Cc. each	
	HTr	N	99.6	After 4 shakings of 25 Cc. each	
	HTr	N/2	99.6	After 4 shakings of 25 Cc. each	
	HTr	N/4	99.6	After 4 shakings (3×25+10Cc.)	
	HTr	N/8	99.6	After 3 shakings of 25 Cc. each	
	HTr	N/12	99.6	After 3 shakings of 25 Cc. each	
	HTr	N/25	93.8	After 1 shaking of 25 Cc.	
	For complete removal from N/25 acid, 2 shakings.				
	HCl	N/2	90.0	3	75
	HCl	N/4	87.5	3	75
	HCl	N/8	89.9	3	75
Veratrine.....	HTr	N/2	99.0	2	35
	HTr	N/4	98.0	2	35
	HTr	N/8	100.0	1	25
	HCl	N/2	63.0	6	150
	HCl	N/4	74.2	5	125
	HCl	N/8	78.7	4	100
	Sulph.	N/2	100	1	25
	Sulph.	N/4	100	1	25
	Sulph.	N/8	100	1	25

VI. SUMMARY.

1. The most practical method for the determination of alkaloids involves the extraction of the alkaloid from an aqueous solution by means of an immiscible solvent, such as chloroform or ether.

2. It further involves the purification of the alkaloidal solution by removal of gums, colors, etc., by similar methods.

3. Unless conditions are carefully guarded, loss of alkaloid as salt or in the free state will occur during the extraction.

4. The equilibrium conditions for the following systems have been established, in the case of the alkaloids aconitine, atropine, brucine, cinchonidine, cinchonine, cocaine, codeine, morphine, quinine, strychnine, and veratrine:

(*a*) The alkaloidal tartrates, tartaric acid, water and chloroform.

(*b*) The alkaloidal tartrates, tartaric acid, water and ether.

(*c*) Certain alkaloidal sulphates, sulphuric acid, water, and chloroform.

(*d*) Certain alkaloidal sulphates, sulphuric acid, water, and ether.

(*e*) Certain alkaloidal hydrochlorides, hydrochloric acid, water, and chloroform.

(*f*) The extraction factors have been determined for all these systems, as well as those described in the literature, and the most favorable conditions for extraction calculated.

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